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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	20

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,647	LAWTON ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 21, 2003 has been entered. Applicant's amendment and response is acknowledged. Claims 1-3, 5 and 7-9 have been amended.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following rejections are withdrawn:

a) Rejection of claims 1-9 under 35 U.S.C. 102(a), pages 8-10, paragraph 6, of the Final Office action mailed January 24, 2003.

b) Rejection of claims 1-9 under 35 U.S.C. 102(b), pages 10-12, paragraph 7, of the Final Office action mailed January 24, 2003.

Rejection Maintained

3. The rejection under 35 U.S.C. 112, first paragraph (written description) is maintained for claims 1-9 for the reasons set forth pages 2-5, paragraph 4 of the Final Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*

The specification broadly describes as a part of the invention a composition and an article of manufacture comprising the isolated polypeptide of SEQ ID No: 2 and variants thereof. The specification states that "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). Applicant has broadly described the invention as embracing any substitution, insertion or deletion change of amino acids throughout the length of the polypeptide sequence. Variants of SEQ ID No:2 correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant urges that the claims recite polypeptides that consist essentially of SEQ ID NO:2 and specified variants of SEQ ID No:2. Applicant urges that SEQ ID NO:2 is 20 amino acids long and the specification teaches that the invention provides having at least 85% identity more preferably 90% identity and still more preferably 96%-99% identity to a polypeptide sequence shown in SEQ ID Nos. 1-7. Applicant asserts that the genus of polypeptides as claimed is not highly variant. Applicant refers to the teachings of Bowie et al which teaches construction of variants and tolerance of protein sequences of substitutions. Applicant urges that there is no absolute requirement for a structural description under the Written Description requirement. Applicant urges that given the teachings of the specification and the prior art (Bowie et al, 1990, Johnson et al, 1993, Karlin et al, 1990, Atschul, 1991 and Branden and Tooze, 1991) it is clear that Applicants were in possession of polypeptides consisting essentially of about 20 amino acids of SEQ ID NO: 2 or a phenotypically silent or conservative amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. Applicant urges that the written description requirement under 35 U.S.C. 112, first paragraph is satisfied.

Applicant's arguments filed June 24, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to that the specification is enabled for the full scope of the claims and therefore does not meet the written description requirement as set forth in 35 U.S.C. 112, first paragraph. The specification broadly describes a genus of isolated polypeptides. Applicant has provided no structural description accompanying the variant language (i.e.

phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-Ehrlichia antibody) recited in the claims. The specification discloses SEQ ID NOs: 1-7. The specification also refers amino acid sequences that are 85% identical to the reference sequence. It is true, there are many reference in the prior art such as *Bowie et al, Johnson et al, 1993, Karlin et al, 1990, Atschul, 1991 and Branden and Tooze, 1991*, that teach the construction of amino acid variants and the use of conservative substitutions, however the requirement under 35 U.S.C. 112, first paragraph written description requires that Applicant's were in possession of the claimed polypeptides at the time of filing. Applicant were in possession of the polypeptide as set forth in SEQ ID NO:2 . However, there is no requirement under 35 U.S.C. 112, first paragraph that requires "one of skill in the art to find polypeptides that are phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody". What are the specific locations in which substitutions can be made to obtain a polypeptides that possess the same or similar characteristics to SEQ ID NO:2? The specification has not shown any specific examples of the claimed phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. While the use of mutagenesis techniques and mathematical algorithms are known in the art, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the

instant disclosure. Therefore, only SEQ ID NO: 2 and not the full breadth of the claim (i.e. phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody SEQ ID NO:2) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

4. The rejection under 35 U.S.C. 112, first paragraph (enablement) is maintained for claims 1-9 for the reasons set forth pages 5-8, paragraph 5 of the Final Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and an article of manufacture that comprise SEQ ID No:2, does not reasonably provide enablement for a composition or an article of manufacture that comprise variants of SEQ ID. No:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are directed to a composition and a article of manufacture comprising the isolated polypeptides of SEQ ID NO: 2 and variants thereof.

The specification is enabling only for the polypeptides of SEQ ID NO:2 as disclosed in the specification. The specification states that "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). The specification teaches that there are many tolerable and conservative amino acid substitutions which can be made that are not critical to protein function (pages 7-9). There is no guidance provided as to which amino acids can be added, deleted or substituted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure

relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other antigens having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are variants of SEQ ID NO: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicant urges that the specification provides ample guidance for one to make and use the invention. Applicant urges that structural description is not required for enablement. Applicant urges that the requirement for enablement is that one can make and use the invention given the specification and coupled with the information known in the art without undue experimentation. Applicant urges that the specification teaches variants that are at least 85% identical to SEQ ID NO:2. Applicant refers to the teaching of the prior art for example *Bowie et al, Johnson et al, 1993, Karlin et al, 1990, Atschul,*

1991 and Branden and Tooze, 1991, that teach the construction of amino acid variants and the use of conservative substitutions. Applicant reference Bowie et al in particular for the teaching that " an amino acid sequence encodes a message that determines the shape and the function of a protein and this message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity". Applicant urges that the specification and the prior art enables one to make and use the claimed invention.

Applicant's arguments filed June 24, 2003 have been fully considered but they are not persuasive. The claims as amended encompass isolated polypeptides that are phenotypically silent amino acid substitution variants of SEQ ID NO:2, each specifically binding to an anti-*Ehrlichia* antibody. The specification does not provide enablement for the full scope of the claimed invention. Applicant has provided no structural description accompanying the variant language recited in the claims.

Applicant urges that that structural description is not required for enablement. The Examiner disagrees with this assertion. The requirement for enablement is that one can make and use the invention given the specification and coupled with the information known in the art without undue experimentation. How can one skilled in the art make and use the claimed composition of matter or article of manufacture comprising phenotypically silent amino acid substitution variants of SEQ ID NO:2 if there is no structural description associated with these substitution variants?

While recombinant, mutagenesis techniques and the use of mathematical algorithms are known, it is not routine in the art to screen multiple substitutions or

multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar anti-*Ehrlichia* antibody binding activity are limited in any polypeptide and the result of such modifications is unpredictable. One skilled in the art would not expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptide is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides. The specification has not shown any specific examples of the claimed phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. It must be remembered that there is no requirement under 35 U.S.C. 112, first paragraph that requires "one of skill in the art to find polypeptides that are phenotypically silent amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody". Therefore a structural description is required. One skilled in the art would require guidance in order to make and use the claimed composition of matter or article of manufacture comprising phenotypically silent amino acid substitution variants of SEQ ID NO:2 commensurate in scope with the claims.

5. The rejection under 35 U.S.C. 102(b) is maintained for claims 1-9 for the reasons set forth pages 13-15 paragraph 8 of the Final Office Action.

The rejection was on the grounds that Rikihisa et al teach immunogenic compositions comprising the isolated polypeptide of SEQ ID NO:2 and pharmaceutically acceptable adjuvants (page 12). Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* (page 17). The polypeptide of SEQ ID No: 2 is disclosed in Figure 19A). The article of manufacture (i.e. dot blot used in the dot blot

analysis) would be inherent in the teachings of the prior art. It is well known in the art to include packing material that comprises a label to indicate the intended use of the article of manufacture. The composition and article of manufacture of Rikihisa, et al appears to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition and article of manufacture with the composition and article of manufacture of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition and article of manufacture of the prior art does not possess the same material structural and functional characteristics of the claimed composition and article of manufacture). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Rikihisa et al do not teach or suggest the use of polypeptides consisting essentially of the about 20 amino acid polypeptide of SEQ ID NO: 2 or phenotypically silent or conservative amino acid substitutions variants of SEQ ID No:2 that specially bind to an anti-*Ehrlichia* antibody. Applicant urges that Rikihisa relates to a complete 288 amino acid protein sequence, that is a full-length protein. Applicant urges that the instant claims recite a polypeptide fragment of about 20 amino acids. Applicant urges that instant specification teaches that the use of these polypeptide fragments provide a sensitivity and selectivity advantage over the use of whole proteins. Rikihisa et a do not teach each and every element of the claimed invention and it does not teach, suggest or inherently disclose the unexpectedly enhanced function afford by the polypeptide fragments of the present invention.

Applicant's arguments filed June 24, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the claimed composition and article of manufacture differs the composition and article of manufacture of the prior art. The claims are drawn to composition and

article of manufacture consisting essentially of an isolated polypeptide shown in SEQ ID NO:2 or a phenotypically silent amino acid substitution variant thereof. Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* (page 17). The claimed invention encompass variants of SEQ ID NO: 2, therefore one skilled in the art could reasonably conclude that the *E. canis* polypeptides of the prior art are variants of SEQ ID NO:2 since Rikihisa et al teach that the invention embraces non-naturally occurring allelic forms or derivatives of the outer membrane proteins (i.e. P30) (page 10) and Rikihisa et al claim isolated polypeptides that are at least 85% homologous to the amino acid sequence shown in Figure 19 (claim 20, page 19). It should noted that the polypeptide of SEQ ID No: 2 is disclosed in Figure 19B (amino acid residues 61-79) and represents a polypeptide that is at least 85% homologous to the amino acid sequence shown in Figure 19. Applicant has provided no side-by-side comparison to show that the claimed polypeptide differs from the *E. canis* polypeptides of the prior art. The prior art teaches composition and article of manufacture consisting essentially of a phenotypically silent amino acid substitution variants of SEQ ID NO:2. Therefore, Rikihisa et al anticipate the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 are indefinite because the claims recite "an isolated polypeptide shown in SEQ ID No:2". It is unclear as to what the Applicant is referring?

7. Claims 1-9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 are indefinite because the claims recite "phenotypically silent substitutions variants". It is unclear as to what the Applicant is referring?

8. Claims 5 and 9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5 and 9 are indefinite because it is unclear as to whether the Applicant is claiming a product or process. Clarification is required.

9. Claims 5 and 9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5 and 9 are indefinite because they recite "under conditions". It is unclear as to what the Applicant is referring?

10. No claims allowed.

Conclusion

11. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
October 21, 2003

MARK NAVARRO
PRIMARY EXAMINER